REMARKS

FORMAL MATTERS:

Applicants thank the examiner for his consideration and entry of Applicants' previous amendment, and the withdrawal of rejections based wholly or partly on the Lee *et al*. With entry of this paper, claims 1, 7, 8, 12-16, 25, and 28-34 are pending and stand as rejected by the Examiner. Claims 1, 7, 12, 13 and 25 have been amended. Support for the amendments to claims 1 and 25 may be found in paragraph [0052] of Applicants original specification. Amendments to claims 7, 12 and 13 are found in the original claims and are made for clarity and/or to better identify the claimed invention consistent with the suggestions made by the examiner in the instant Office Action. No new matter has been added.

Applicants respectfully request reconsideration of the pending rejections in light of the claim amendments and remarks presented with this paper.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1 , 7, 8, 12-16, 25 and 28-34 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1 - 14 of copending Application No. 11/193,318. The rejection is provisional because the allegedly conflicting claims have not been patented. With this paper, Applicants have filed a terminal disclaimer obviating the instant rejection. Applicants therefore respectfully request the rejection be withdrawn.

REJECTIONS UNDER §112

Claims 1, 7-8, 12-16, and 28-34 are rejected under 35 U.S.C. 112 first paragraph as allegedly failing to comply with the written description requirement. According to the Office Action, Applicants' specification fails to teach "more efficient" electron transfer. The Office Action states that paragraph 0055 (0052) implies that moving the redox moiety closer to the electrode results in a signal on process, but none of

the cited paragraphs teach "more efficient" electron transfer. The Office Action goes on to criticize support provided by figures 2 and 3 through creation of hypothetical structures that do not exist in Applicants specification. This rejection is respectfully traversed as applied to the pending claims.

The rejection appears to be based solely on the Examiner's failure to find the phrase "more efficient" in the support cited by Applicants in their previous response. Applicants respectfully point out that there is no *in haec verba* requirement with regard to claim amendments and what the specification to the application "teaches." The correct standard is whether Applicants' specification supports the claim amendment through express, implicit, or inherent disclosure. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998). See also *In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989)

Applicants have amended the claims at issue to more clearly articulate the invention. The rate (and thus efficiency) with which an electrode-coupled redox moiety transfers electrons to provide a residual current is exponentially distance-dependent. As the proximity of the redox moiety to the electrode is reduced, the efficiency of electron transfer is increased leading to a larger current noted as the "signal on" effect in Applicants' invention. Applicants respectfully submit that one of skill in the art would readily understand Applicants' specification as describing this process. For example claim [0052] of Applicants' specification reads:

> "In another embodiment, as shown in FIG. 3, an oligonucleotide probe 30 may be coupled near or to electrode 36 via bond 32. The end of probe 30 **distant from the point of attachment** 32 is labeled with redoxable moiety 34. **In the absence of**

> **target 38, probe 30 is "open" and label 34 is a long distance from electrode 36**. In this embodiment, probe 30 contains regions 31 and 33 which are complementary to regions 35 and 37 on target 38. **When target 38 and probe 30 are hybridized**, target 38 bridges regions 31 and 33 of probe 30 to form loop 40, and thus **positions redoxable moiety 34 in sufficient proximity to electrode 36 to promote electron transduction**, which can be detected." Emphasis added.

Thus even if one were to take the extreme position that the probe conformation in the absence of target 38 produces no electron transduction and in the presence of target 38 produces maximal electron transduction, it can only be concluded that movement from the former to the latter conformation increased the efficiency of electron transduction. There is no other logical result based on an understanding of the electrochemical processes involved that where well known in the art.

Applicants further point out that the originally filed claims included the phrase;

> "…in the absence of hybridization between the target and the probe, at least one redox moiety being located in a first position relative to the electrode and, in the presence of hybridization between the target and the probe, said at least one redox moiety being located in a second position relative to the electrode, **said first and second positions giving rise to distinguishable redox events detectable by the electrode** wherein the second position is closer to the electrode than the first position." From original claim 1, Emphasis added.

Applicants therefore respectfully submit that the language presented in the original claims supports the concept of different electron transfer efficiencies between the first and second positions of the redox moiety associated with probes of Applicants' invention, as recited in the claim amendments at issue.

As to the hypothetical alternatives to the figures in Applicants' specification presented in the Office Action, Applicants respectfully point out that the Office Action

fails to identify any disclosure of the hypothesized alternatives in Applicants' specification, and the suggested structures are contrary to the descriptions of the figures found in paragraphs [0051] and [0052] of Applicants' specification. Therefore Applicants' respectfully submit that the alternative structures presented in the Office Action find no place in a discussion of what Applicants' specification "teaches."

Accordingly, Applicants do not feel that the claims at issue require amendment to comply with the written description requirement of 35 U.S.C. 112. Nonetheless, in the interest of expedient prosecution and comity, Applicants have amended claims 1 and 25 to include the phrase, "promotes electron transduction" as expressly presented in Applicants' specification. In view of the arguments presented above, Applicants respectfully submit the instant rejection should be withdrawn.

Claims 12 and 13 are rejected under 35 U.S.C. second paragraph as allegedly failing to particularly point out and distinctly claim the invention.

Applicants thank the Examiner for his suggestions and have amended the claims at issue accordingly. Applicants therefore respectfully request the rejection be withdrawn.

REJECTIONS UNDER §103

Claims 1, 7-8, 12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn *et al.*, (U.S. Patent No.: 6,264,825 B1, issued July 24, 2001) in view of Lizardi *et al.*, (U.S. Patent No. 5,312,728, issued May 17, 2002).

Establishing a *prima-facie* case for obviousness under §103 requires the Examiner show, *inter alia*, that the prior art references taken together teach or suggest all claim limitations of the rejected claim(s). *In re Royka*, 180 USPQ 580 (CCPA 1974); and MPEP §2143.03. Applicants respectfully submit that the suggested combination fails to teach all of applicants claim limitations and therefore fails to present a *prima-facie* case of obviousness. In particular, the combination fails to teach a probe directly bound to an electrode and comprising a redox moiety.

The Office Action characterizes Blackburn as teaching a probe that is ***both*** immobilized on an electrode ***and*** comprises a redox moiety, as presented in Applicants' claims. Applicants respectfully submit that the characterization presented in the Office Action is in error as it borrows characteristics from several different components of the reference, and attempts to combine these into a single component. Applicants urge that such an exercise not only fails to support a prima-facie case of obviousness, but also could only be undertaken in hindsight using Applicants' specification as a road map. Combination of Blackburn with Lizardi does not cure the deficiencies in Blackburn because Lizardi does not use probes attached to electrodes for electrochemical detection of target molecules.

The Office Action cites to col. 13, lines 10-13, and col. 41, lines 17-25 of Blackburn et al. as support for probes attached to an electrode. Applicants respectfully point out that the citation to col. 13 refers to electrophoresis electrodes, not detection electrodes, and is silent as to attached probes. The citation to col. 41 discusses attachment of "conductive oligomers" to an electrode. The "conductive oligomer" is not a probe *per se*, but is described in the preceding paragraph as a link between the electrode and a "capture probe." There is no mention of either "conductive oligomers" or "capture probes" comprising a redox moiety as presented in Applicants' claimed invention.

The Office Action next turns to Col. 66, lines 9-44 as allegedly disclosing probes comprising redox moieties (ETMs). The probes discussed in Col. 66 however are "amplifier probes," not capture probes bound to an electrode. The discussion in the preceding column 65, particularly lines 29-36, identifies amplifier probes as hybridized to target sequences, where the "target sequence is preferably, but not required to be, immobilized on the electrode using capture probes." Thus Blackburn *et al.* clearly identify amplifier probes as being distinct from capture probes, and nowhere does Blackburn identify amplifier probes as being directly bound to an electrode in the manner required in Applicants claimed invention. In fact, from the passage recited immediately above, the only way an amplifier probe may be held in the vicinity of an electrode is

indirectly through hybridization to a target molecule which in turn must be hybridized to a capture probe. (See e.g., Blackburn *et al.* figures 4C and 5E). Therefore, contrary to the characterization presented in the Office Action, Blackburn *et al.* do not teach a probe that is both immobilized on an electrode and comprises a redox moiety as in Applicants' claimed invention. As Lizardi *et al.* fails to discuss electrode-bound probes having a redox moiety in any context, neither of the references sought to be combined in the Office Action teach this element of Applicants claimed invention and therefore the proposed combination fails to support a *prima-facie* case of obviousness against Applicants' invention. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

Further, the Office Action admits that Blackburn *et al.* does not teach that "the end of the probe bearing the redox moiety moves closer to the electrode upon binding the target" as claimed by Applicants. Seeking to overcome this admitted deficiency in Blackburn *et al.*, the Office Action recruits the molecule presented in figure 12 of Lizardi *et al.* and reproduced below. The Office Action seeks to modify the molecule of Lizardi et al., by immobilizing it to an electrode and coupling it to a redox moiety as allegedly taught by Blackburn *et al.* Specifically, the Office Action suggests that the molecule presented in Figure 12 of Lizardi *et al.* could be modified in view of Blackburn to be immobilized at end 35 and a redox moiety added to end 32. Binding of a target molecule would purportedly move end 32 closer to end 35 thereby providing more efficient electron transfer as allegedly suggested in Figure 13 of Lizardi *et al.*, also produced below.

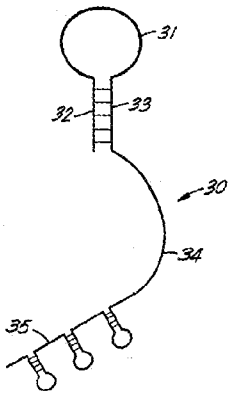

FIG.12

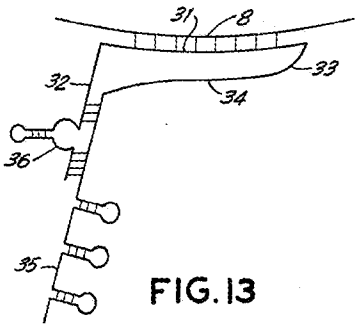

FIG.13

The Office Action attempts to find motivation to make this modification by suggesting it "...would have resulted in a detector having the added advantage of having probes that allow production of a billion copies of a potentially scarce target in a single step amplification of as explicitly taught by Lizardi *et al.* (column 3, lines 48-50)."

As Applicants have already pointed out, neither Blackburn *et al.* nor Lizardi *et al.* teach a probe that is both directly bound to an electrode and includes a redox moiety. Therefore the basis upon which the proposed combination is based is factually flawed in a manner fatal to the proposed combination. As neither reference individually or combined teaches a probe having a redox moiety and being directly bound to an electrode as required by Applicants' claims, the references can not render Applicants' invention obvious.

Furthermore, Applicants respectfully point out that practicing the invention in a manner providing the suggested motivation for making the combination in the first place renders the invention useless. Proposed modifications that render the prior art invention being modified unsatisfactory for its intended purpose do not provide the requisite suggestion or motivation to make the proposed modification necessary to support a *prima facie* case for obviousness. MPEP 2143.01 V.; *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). A thorough reading of Lizardi *et al.* reveals that the single-step amplification identified as motivation to combine the references is a consequence of linking an RNA that is known to be copied in an exponential fashion by an RNA-directed

RNA polymerase to the DNA "switch" molecules, such as the ones depicted in figures 12 and 13, above. (See Col 3, line 3 *et seq.*). Lizardi *et al.* however suggest that this approach leads to non-specific binding prior to amplification that is addressed by RNA cleavage. (See Col. 4, line 8 *et seq.*). Applicants respectfully point out that signal "amplification" in Applicants' claimed invention is dependent upon the number of probes immobilized to the electrode. Incorporation of an RNA segment into Applicants' invention with subsequent cleavage, as suggested by Lizardi *et al.*, would release either Applicants' probe from the electrode or the redox moiety from the probe, rendering the invention inoperable. Assuming, *in arguendo*, that the Office Action was correct in its characterization of the molecules of Blackburn et al., the combination suggested in the Office Action would suffer the same fate. Therefore, practice of the combination in the manner suggested by the Office Action would render the combination useless. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn *et al.*, (U.S. Patent No.: 6,264,825 B1, issued July 24, 2001) in view of Lizardi *et al.*, (U.S. Patent No. 5,312,728, issued May 17, 2002, and further in view of Rothberg *et al.*, (U.S. Patent Application Publication No. US 2002/0012930 Al, published 31 January 2002).

As explained above, the combination of Blackburn *et al.* and Lizardi *et al.* fails to teach or suggest all limitations to Applicants' claimed invention. Rothberg *et al* is characterized by the Office as disclosing probes hybridized to targets wherein the probe and the target have a loop during hybridization, wherein the hybridized rolling circle probe leaves a loop in the target in the form of the gapped region and a loop in the form of the single stranded portion of the rolling circle template molecule. Rothberg *et al* allegedly disclose the loop in the target has the added advantage of allowing detection of single nucleotide polymorphisms in the gap. Rothberg *et al* further disclose the rolling circle probe has the added advantage of allowing isothermal amplification to generate thousands of copies of the target nucleic acid.

Assuming, for the sake of discussion, the above characterization of Rothberg is accurate, the Rothberg reference fails to address the deficiencies in the combination of Blackburn *et al.* and Lizardi *et al.* as previously explained. Therefore the proposed combination cannot teach each limitation of Applicants' invention and accordingly cannot render Applicants invention obvious.

Specifically, nothing in Rothberg *et al.* suggests or teaches Applicants' limitation regarding a probe comprising a redox moiety and immobilized on an electrode. Therefore, Applicants respectfully submit that the proposed combination of Blackburn *et al.* and Lizardi *et al.* with Rothberg *et al.* fails to teach or suggest all of Applicants claim limitations. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. Applicants have amended claims withdrawn as a consequence of the earlier restriction requirement to provide the limitations of the currently prosecuted claims. Accordingly, Applicants request rejoinder of withdrawn claims pursuant to MPEP §821.04, and examination pursuant to 37 C.F.R. §1.104.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSB-510CIP.

Respectfully submitted,
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Enclosure: Terminal Disclaimer

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